Head and Neck Steering Committee Strategic Priorities 2019

Head and neck squamous cell carcinoma (HNSCC) accounts for approximately four percent of all cancers in the United States and is the sixth leading incident cancer worldwide. In the United States, it is estimated that 65,410 new cases (48,000 men and 17, 410 women) and 14,620 deaths from HNSCC will occur in 2019. (https://www.cancer.net/cancer-types/head-and-neck-cancer/statistics). Despite advances in surgical and radiotherapy techniques, as well as integration of chemotherapy into multimodality treatment paradigms, HNSCC is highly morbid and frequently lethal. Five-year overall survival (OS) for local regional advanced HNSCC is approximately 65%. Although HNSCC is a predominant focus, the mandate of the Head and Neck Steering Committee also extends to treatment of thyroid, salivary gland, skin, and other rare cancers of the head and neck. This mandate also includes vulnerable populations who may not have been regularly offered clinical trials in the past (e.g. the increasing population of elderly patients).

The most common HNSCC are now subdivided by their principal causal factors: oral human papillomavirus (HPV) infection versus the classical risk factors of heavy exposure to tobacco and alcohol. HPV-positive cancers are rapidly increasing in incidence and are also associated with improved survival after treatment with all conventional treatments, including surgery, cisplatin chemotherapy, and radiation. Despite this, treatment strategies for this subset of HNSCC remain unresolved, particularly for de-intensification approaches. In contrast, HPV-negative HNSCC remains associated with a poor prognosis, despite treatment intensification. Both forms of HNSCC represent the consequence of a fundamental failure of regulation of cell growth and survival as well as immune surveillance, tumor recognition and destruction. HNSCC has long been recognized as an immunosuppressive disease, including defects in the major effector cells of innate and adaptive immunity.

Currently available treatment options for HNSCC consist of surgery, radiation and chemotherapy, administered in single or multi-modality regimens. However, these treatments still leave room for substantial improvement in efficacy, particularly for HPV-negative HNSCC. Due to unique epidemiological, anatomical, and clinical characteristics, HNSCC represents an ideal model among epithelial malignancies for testing clinical trials concepts and novel agents. In this regard, immunotherapy has emerged as a promising, fourth treatment modality in cancer treatment. First generation immunotherapeutic agents are now approved for platinum refractory and recurrent/metastatic HNSCC. The clinical benefit of the addition of these agents to the treatment of locally advanced disease is an active area of investigation. Molecularly targeted therapies that address pathways of pathophysiological significance have led to the development of approved agents for HNSCC, thyroid and rare salivary gland cancers and new targets are anticipated from ongoing genomic analyses.

Current conventional multimodality therapies are often associated with worsened quality of life post-treatment, with toxicities that can include xerostomia, dysphagia, and tissue fibrosis. Standard multimodality regimens designed for aggressive tobacco-related HNSCC likely represent overtreatment of HPV-positive HNSCC patients with a good prognosis. Thus, acute and long-term toxicities are a major concern for a subset of HPV- positive cancer patients at low-risk who are, fortunately, expected to have long-term cancer control.

Since most HPV-associated HNSCC patients manifest very good prognosis, an emerging issue has been the identification of patients that may be appropriate for decreased treatment intensity. In this regard, a national priority in HPV-positive HNSCC is the development of rational de-intensification strategies that preserve the high

cure rate while sparing the toxicity. Studying patients with good prognosis and/or early stage disease presents an opportunity for more targeted therapy, or less intensive treatment using conventional modalities. These approaches include limited or minimally invasive surgical resection; alterations in radiation modality, target volumes, dose/fractionation schedules and timing; alterations in systemic therapy type, dose and schedules. Use of novel molecularly targeted agents may also lead to effective treatments with less toxicity.

Although incidence rates for HPV-negative HNSCC are declining in the United States, the morbidity and mortality associated with these cancers remains devastating. Novel therapeutic approaches for these cancers are of critical importance.

The overall goal of the Head and Neck Steering Committee of the National Clinical Trials Network (NCTN) is to approve clinical trials with potential to improve survival, decrease morbidity and enhance quality of life of patients affected by head and neck cancers. Our priority is to support randomized clinical trials that achieve these aims and change the standard of practice. However, we acknowledge that in some instances such as in very rare tumors or molecularly defined subsets, such trials are not feasible. Therefore, alternative clinical trials that are designed to demonstrate a meaningful clinical benefit in outcome in comparison to a historical control may be appropriate. In some circumstances, even historical data may be limited, and single arm trials to establish normative data may be considered.

In the context of the Committee's principal goals, important trial design features may include testing of biomarker-driven (e.g. genomic or immunologic profiling) treatment algorithms with existing or new therapeutic agents. The Committee encourages the incorporation of quality of life and patient reported outcome measures into clinical trials.

Enumerated without preference, current Strategic Priorities for NCTN treatment trials under the auspices of the Head and Neck Steering Committee are:

1. Design treatment trials to improve efficacy and survival, decrease morbidity, and increase quality of life for all treatment interventions and modalities.
    a. Improve the efficacy, application, and cost-effectiveness of focused radiotherapy techniques (such as IMRT, IGRT, SBRT, and particle beam therapy).
    b. Improve the efficacy and application of modern surgery (such as TORS and other minimally invasive approaches).
    c. Improve the efficacy and application of systemic therapies (such as targeted therapies and immunotherapy).
    d. Rigorously test strategies aimed at minimizing treatment-related morbidity without impairing oncologic outcomes.
    e. Within these trials collect robust patient reported outcomes, and rigorously design correlative laboratory studies.
2. Develop trials for treatment-resistant head and neck cancer.
3. Pursue trials of rare tumors arising about the head and neck, which can only be undertaken through the NCTN.